A STUDY ON THYROID DYSFUNCTION IN HIV INFECTED INDIVIDUALS

Dissertation submitted in partial fulfillment of
Requirements for

M.D.DEGREE IN GENERAL MEDICINE
BRANCH - I

of

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI

GOVERNMENT KILPAUK MEDICAL COLLEGE
CHENNAI - 10

APRIL 2011

BONAFIDE CERTIFICATE

This is to certify that "A STUDY ON THYROID DYSFUNCTION IN HIV INFECTED INDIVIDUALS" is a bonafide work done by Dr.Aparna.S, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of The Tamilnadu Dr.M.G.R. Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2008 to April 2011.

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ACKNOWLEDGEMENT

At the outset I thank Prof. ***V. Kanagasabai, M.D.,*** Dean, Kilpauk Medical College, for having permitted me to use the hospital resources for the study.

I am extremely grateful to ***Prof. Dr. G. Rajendran,*** Professor and Head of the Department of Internal Medicine, Kilpauk Medical College, Chennai for permitting me to carryout this study and for his constant encouragement and guidance.

I owe my sincere gratitude to my ***chief Prof. N. Raghu***, ***MD.***, Department of Internal Medicine, Kilpauk Medical College, Chennai for his inspiration, advice, comments, corrections and guidance in making this work complete.

I also express my sincere gratitude to ***Prof. A. Joseph Navaseelan, MD., Prof. D. Varadharajan, MD., and Prof. B. Chellam, MD., Prof. M.D. Selvam, MD.,*** for their help and guidance rendered during the entire period of my work.

I express my deep gratitude to ***Dr. R. Kulothungan, MD., Dr. S. Parimalasundari, MD., and Dr. M. Malarvizhi, MD.,*** Assistant Professor, Department of Internal Medicine, Kilpauk Medical College, Chennai for their inspiration, advice, comments, corrections and guidance in making this work complete.

I whole heartedly express my sincere thanks to ***Dr. K. Nandagopal, DV.,*** Medical Officer, ART centre, Kilpauk Medical College, Chennai for his valuable guidance and support throughout my dissertation work.

I also extend my thanks to all the laboratory technicians, staff and statistician in Kilpauk Medical College, Chennai for their valuable support throughout my dissertation work.

I also thank my family members, colleagues and friends for their moral support and encouragement throughout my dissertation work.

Last but not the least, with sincere gratitude I thank all the patients who contributed so much to this study without whom this study could not have been possible.

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INTRODUCTION

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Acquired Immuno Deficiency Syndrome was first recognized in the United States in 1981 when the U.S Centre for Disease Control and prevention (CDC) reported unexplained occurrence of Pneumocystis jiroveci pneumonia in five previously healthy homosexual men. Within months, disease was recognized in injection drugs users (IDUs), in recipient of blood transfusions and hemophiliacs.

In 1983, Human Immuno Deficiency Virus was isolated from a patient with lymphadenopathy and in 1984 it was demonstrated clearly to be the causative agent of AIDS.[1] India's first case of AIDS was reported in 1986 from Chennai.[2]

Human immunodeficiency virus (HIV) infection can lead to multiple organ involvement including the endocrine system. Endocrine function may be altered in these subjects because of the possible relationship between the immune and endocrine systems, direct involvement of the glands by the HIV itself, opportunistic infections or malignancies.[3&4]

Abnormal thyroid functions in these patients may be caused by the stress of advanced disease or concomitant morbidities and may manifest

as the classic sick euthyroid syndrome probably due to a hypothalamic pituitary deficit related to the progress of immunodeficiency and cachexia.[3] Cytokines such as IL-6 and TNF-α can acutely decrease TSH and T3 and increase rT3 levels. LoPresti et al studied thyroid functions in HIV positive patients, to evaluate if they could be used to predict their progression and outcome.

Jain et al reported abnormal thyroid levels which correlated with the CD4 counts and severity of the disease.[5]

Screening studies have demonstrated an increased prevalence of primary hypothyroidism in HIV infected patients. Beltran4 reported overt hypothyroidism in 2.6%, subclinical hypothyroidism in 6.6% and an isolated low T4 level in 6.8% of 350 subjects studied. Low free T4 levels (1.3%) and subclincal hypothyroidism (3.5%) which correlated with low CD4 counts were reported in a Spanish population.[6]

An infectious trigger for immune activation (by molecular mimicry) is one of the postulated mechanisms for autoimmune disease. However hypothyroidism in HIV infected patients is not associated with autoimmunity.10 one case of Hashimoto's hypothyroidism has been reported so far after highly active anti-retroviral therapy (HAART) initiation.[7]

Subclinical hypothyroidism is more prevalent in the HIV infected population, compared to HIV-negative individuals.[8&9] Quirino[8] reported a similar prevalence of subclincal hypothyroidism in both naive and HAART treated subjects,

Beltran et al[12] found that subclinical hypothyroidism was associated with the use of stavudine and lower CD4+ cell count, The cumulative daily dose of both stavudine and lamivudine was significantly related to the presence of hypothyroidism in Grappin's series.[9] Didanosine and ritonavir were associated with a low free T4.

Madge et al [10] found the prevalence of hypothyroidism to be 2.5% (overt) and 4% (subclinical). Hyperthyroidism (overt and subclinica) l occurred in <1%.of patients.

Nelson's study[11] revealed a higher than expected incidence of overt hyopothyroidism in patients receiving HAART and they recommend universal screening of subjects on therapy.

Inview of abnormal TFT encountered often in HIV positive individuals and HIV patients on HAART, it was decided to undertake a study of thyroid function on HIV infected patients at Kilpauk Medical College Hospital, Chennai.

AIMS OF THE STUDY

- To study the prevalence of thyroid dysfunction in HIV infected patients.

- To compare thyroid dysfunction in pre ART HIV individuals with individuals on HAART.

- To study thyroid function test in patients with HIV at various stages of illness and co-relate their results with disease progression.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HIV evolved from simian immunodeficiency virus (SIV) in chimpanzees and monkeys. Surprisingly, in its natural host, SIV does not cause disease, despite replicating to high levels in infected animals. This lack of pathogenicity may be from a lack of T cell activation in these hosts.

Alternatively, these species may have developed tolerance to the infection through natural selection.[13&14] Data suggest that humans acquired HIV type 1 (HIV-1) from Pan troglodytes troglodytes chimpanzees infected with SIV, and that HIV-1 was introduced into the human population (as SIV) from these chimpanzees on at least three independent [15] HIV-2 originated from the sooty mangabey monkey (Cercocebus atys).[16]

Since its identification in early eighties, HIV has attained epidemic proportions inspite of it being designated as biosafety level 2 pathogen.[17] The distribution of the spread is such that its incidence is racing alarmingly in Sub-Saharan Africa, South and South East Asia, eastern Europe whereas prevalence is on the rise in the developed nations.

TRANSMISSION

Person-to-person transmission can occur through

- Sexual contact
- Injection drug use
- Contaminated blood products
- Mother-child transmission
- Occupational exposure

PATHOGENESIS AND PROGRESSION OF DISEASE

HIV is a member of the lentivirus family of retroviruses. HIV appears as spherical particles that are approximately 110 nm in diameter, with knoblike projections on the surface of the virus and a cone-shaped viral core. [18] The genome is organized into three major regions (gag, pol, and env) and has six regulatory genes that are vital for its life cycle, and the subsequent exposure of the other HIV envelope protein, gp41.

After the fusion of the viral and cellular membranes, the viral capsid enters the cell and the HIV reverse transcriptase enzyme converts the single- stranded HIV RNA into a double-stranded DNA, which then is integrated with host chromosome by the viral enzyme integrase. Cellular enzymes transcribe the provirus into mRNA

which is then translated into the structural proteins or which serve as genomic RNA for progeny virus. Viral replication involve both the assembly of the viral particles, with each viral core incorporating two copies of the viral RNA genome, and the budding and release of the virus from the cell surface mediated by HIV protease enzyme.

Disease Progression

Shortly after acute HIV infection, HIV begins to preferentially destroy HIV-directed CD4+ helper T cells; this process impairs the critical interaction between host CD4+ T cells and CD8+ T cells and thus weakens the host CTL response. HIV extensively seeds lymphoid organs and the central nervous system. As a result, the infection persists, and continued rounds of replication lead to the gradual depletion of all CD4+ T cells. At the same time, a subset of activated, HIV-infected CD4+ T cells returns to a quiescent state, remains latently infected.[19]

The CD4+ T cell count provides an accurate way to assess the current immunologic status. The plasma HIV RNA level is a strong independent predictor of the progression to AIDS in untreated HIV-infected persons[20] . In essence, the higher the HIV RNA level, the more rapidly the disease will progress.

Clinical Features

Primary Infection

Primary infection is symptomatic in 70-80% of infected individuals and usually occurs 2-4 weeks after exposure. The major clinical manifestations are fever (seen in 80% to 90% of patients), fatigue (70% to 90%), rash (40% to 80%), headache(32% to 70%), lymphadenopathy (40% to 70%), pharyngitis (50% to 70%), and myalgias or arthralgias (50% to 70%).[21] Acute HIV illness typically persists for less than 14 days, but some patients have had illnesses that have extended for longer than 10 weeks. The appearance of specific anti-HIV antibodies in serum takes place later 3-12 weeks later, although very rarely seroconversion may take place after 3 months.

Asymptomatic stage-clinical latency

The median time of this stage is about 10 years during which HIV replication is ongoing and progressive. The rate of disease progression is directly correlated to with HIV RNA levels as stated above. Long-term nonprogressors show little, if any, decline in CD4+ T cell counts. During the asymptomatic phase, the average rate of CD4+ T cell decline is 50/μL per year. When the CD4+ T cell count falls below 200/μL, the resulting immunodeficiency leads to symptomatic disease.

Symptomatic disease-AIDS

Acquired immunodeficiency syndrome (category c disease) is defined by the development of specified opportunistic infections, tumors etc.

Common AIDS – Defining Conditions

- Oesophageal candidiasis
- Cryptococcal meningitis
- Chronic cryptosporidial diarrhea
- CMV retinitis
- Chronic mucocutaneous herpes simplex
- Disseminated mycobacterium avium intercellulare
- Military or extrapulmonary tuberculosis
- Pneumocystis pneumonia
- Cerebral toxoplasmosis
- Kaposi's sarcoma
- HIV encephalopathy/PML
- lymphoma

The listed AIDS defining conditions are as per revised CDC classification (1993) which categorizes persons on the basis of

clinical conditions and CD4+ T-lymphocyte counts[22] For children less than 13 years of age, there is a modified and revised classification system for HIV infection. The World Health Organization (WHO) has also published a staging system for HIV infection. The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

WHO staging of HIV infection

Clinical group-I

- Acute HIV infection
- PGL
- Asymptomatic
- Normal activity

Clinical group-II (Early stage disease)

- Weight loss<10%
- Muco-cutaneous problem
- Herpes zoster
- Recurrent URI
- Normal activity

Clinical group-III (Intermediate disease)

- Weight loss<10%
- Chronic diarrhea
- Prolonged fever 1 month
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infection
- Bed ridden < 50% of day (previous month)

Clinical group-IV (Late stage disease)

- Definitive or presumptive diagnosis of AIDS
- Bed ridden > 50% of day (previous month)

The diagnosis of HIV infection depends upon the demonstration of antibodies to HIV and / or the direct detection of HIV or one of its components.

Diagnosis

The standard screening test of HIV infection is the ELISA, also referred to as enzyme immunoassay (EIA). This solid – phase assay is an extremely good screening test with a sensitivity of >99.5%.

Most diagnostic laboratories use a commercial EIA kit that contains antigens from both HIV -1 and HIV -2 and thus are able to detect either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensitivity to newly discovered species, such as group O viruses. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity.

The most commonly used confirmatory test is the western blot. This assay takes advantage of the fact that multiple HIV antigens of different, well – characterized molecular weight elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the western blot[23].

A negative western blot is one in which no bands are present at molecular weights corresponding to HIV gene products. While the western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20 – 30 % may show one or more bands on western blot. While these bands are

usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RNA PCR, RNA assay, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which is the product of the percent of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count (determined by WBC and differential percent) has been shown to correlate very well with the level of immunologic competence.

Patients with HIV infection should have CD4 + T cell measurements performed at the time of diagnosis and every 3 to 6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to most guidelines, a CD4+ T cell count <350 /µL is an indication of initiating antiretroviral therapy, and a decline in CD4+ T cell count of > 25% is an indication for considering a change in therapy.

ANTIRETROVIRAL THERAPY

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast and short-lived trends. Since the introduction of zidovudine as monotherapy in 1987, the treatment options have grown rapidly.

Research has unleashed an array of drugs in each of the class of drugs and newer classes of drugs are fast coming upon the horizon.

Currently, four different classes of medications, target HIV:

(1) nucleoside reverse transcriptase inhibitors (NRTIs)—

abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate (tenofovir-DF), zalcitabine, and zidovudine;

(2) nonnucleoside reverse transcriptase inhibitors (NNRTIs)—

delavirdine, efavirenz, and nevirapine;

(3) protease inhibitors

atazanavir, fosamprenavir, indinavir, lopinavir plus ritonavir, nelfinavir, ritonavir and saquinavir

(4) fusion inhibitors

Enfuvirtide

Newer drugs and classes of drugs that have or about to join these popular drugs are

New nucleoside analogs

- ❖ Elvucitabine, Nicavir, Racivir, Stampidine

New NNRTIs

- Etravirine, Rilpivirine

New protease inhibitors (PIs)

- ❖ Darunavir, Brecanavir

Coreceptor antagonists - CCR5 antagonists.(30)

- ❖ Maraviroc, Vicriviroc

Integrase inhibitors

- ❖ Raltegravir[24]

Other drugs in the pipeline are –

- ❖ Maturation inhibitors
- ❖ Fusion inhibitors
- ❖ Attachment inhibitors
- ❖ Entry inhibitors.

Mechanism of action

The NRTIs—also known as nucleoside analogues—structurally resemble the human nucleosides that HIV uses to make viral DNA. The HIV reverse transcriptase enzyme can mistakenly incorporate the synthetic nucleoside analogue into the elongating strand of viral DNA during the reverse transcriptase process; once incorporated into viral DNA, the nucleoside analogues act as chain terminators because they lack the 3′ hydroxyl group required for chain elongation.

The NNRTIs do not act as chain terminators; rather, they directly inhibit the proper functioning of the reverse transcriptase enzyme.

The HIV protease inhibitors selectively bind to HIV protease and prevent this enzyme from performing its normal function of cleaving viral polyprotein precursors into individual functional proteins.

The fusion inhibitor works by binding to the gp41 envelope protein of HIV to prevent it from mediating fusion of the viral and cell membrane

HAART – IT'S IMPLICATIONS

The term 'highly active antiretroviral therapy' gained widespread acceptance since 1996 when the new class of protease inhibitors were approved for use. Since then HAART has maintained itself as the first line of defence against HIV infection. Traditionally HAART consists of combination of three or more drugs in any of the following class, not necessarily in the same order:

NRTI + NRTI + NRTI / NNRTI / PI

In the earlier phase HAART was shown to reduce, between 1994 and 1998, the incidence of AIDS in Europe from 30.7 to 2.5 per 100 patient years [25] which was replicated elsewhere.

In 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs [26].

Realization about lipodystrophy, a new term, followed by mitochondrial toxicity [27] reinforced the dictum: all effective drugs have side effects. The initial euphoria over eradication of viral load with HAART has turned bleak with HIV remaining detectable in latently infected cells, even after long-term suppression and the most recent estimate for eradication of these cells standing at 73.3 years[28] This has led

us to coexist with the spectrum of dramatic improvement in the standard of living standard of HIV infected individuals on one hand and hitherto unheard of toxicities of associated with daily consumption of loads of drugs on a long term basis. Treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity

Thyroid

The thyroid is one of the largest endocrine glands in the body, weighing approximately 15 to 20 g. The presentation of thyroid conditions can range from clinically obvious to clinically silent. Their consequences can be widespread and serious, even life threatening. Persons of both sex and any age can be affected, although almost all forms of thyroid disease are more frequent in women than in men, and many thyroid ailments increase in frequency with age.

The thyroid dysfunction is simply classified as hypothyroidism, hyperthyroidism, sub clinical hypothyroidism and sub clinical hyperthyroidism depending upon the TSH and thyroid hormone levels.

Clinical status	TSH level	Thyroid hormone
Normal	Normal	Normal
Hypothyroid	High	Low
Hyperthyroid	Low	High
Sub clinical Hypothyroid	High	Normal
Sub clinical Hyperthyroid	low	Normal

Hypothyroidism

Hypothyroidism is the condition resulting from lack of the effects of the thyroid hormone on body tissues. Hypothyroidism is a common condition. [29&30] The overall incidence in the population is approximately 1% to 2 %.[31&32] In both sexes, the incidence increases during and after middle life.[33] The serum TSH levels are more than 10mU/L and associated with low values of thyroid hormones. Florid hypothyroidism can be diagnosed clinically.

The symptoms of hypothyroidism are:

- Tiredness, weakness
- Dry skin
- Feeling cold

- Hair loss
- Difficulty in concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (Later amenorrhea)
- Paraesthesia
- Impaired hearing

The signs of hypothyroidism are as follows

- Dry coarse skin
- Cool peripheral extremities
- Puffy face, hands and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions.

SUBCLINICAL HYPOTHYROIDISM

The term subclinical hypothyroidism designates a situation in which an asymptomatic patient has a low-normal FT4 but a slightly elevated serum TSH level. Other terms for this condition are mild hypothyroidism, preclinical hypothyroidism, biochemical hypothyroidism, and decreased thyroid reserve. The TSH elevation in such patients is modest, even a high normal serum TSH level (e.g., 3.0 µU/L) may reflect very mild thyroid dysfunction, particularly in a patient who has other clinical or laboratory features of autoimmune thyroiditis.

As a result, some authorities have recommended lowering the TSH assay's upper limit of normal to 2.5 µU/L[34] The values typically between 4.25 and 10 µU/L. [35] associated with normal total or free T4 and T3 levels constitute subclinical hypothyroidism as stated in the latest consensus statement by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society.

HYPERTHYROIDISM

Hyperthyroidism is the condition resulting from the effect of excessive amounts of thyroid hormones in the body tissues. Thyrotoxicosis is a synonym. Graves's disease is the most common cause of hyperthyroidism. Approximately 0.5% to 1% of the population suffers from hyperthyroidism. The TSH levels are suppressed, usually < 0.1 mU/L and associated with high levels of thyroid hormones.

The symptoms of hyperthyroidism are as follows:

- Hyperactivity, irritability, dysphoria.
- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight loss with increased appetite
- Diarrhoea
- Polyuria
- Oligomenorrhea, loss of libido

The signs of hyperthyroidism are as follows:

- Tachycardia; Atrial fibrillation in the elderly
- Tremors
- Goitre

- ❖ Warm, moist skin
- ❖ Muscle weakness, proximal myopathy
- ❖ Lid retraction or lid lag
- ❖ Gynaecomastia

SUB CLINICAL HYPERTHYROIDISM

Sub clinical hyperthyroidism is defined as low serum TSH levels (0.1mU/l to 0.4mU/L) associated with normal free T4 and free T3 levels.[36] Sub clinical hyperthyroidism is much less common than sub clinical hypothyroidism. The prevalence is about 2%; it is more common in women, blacks, and the elderly.

NON THYROIDAL ILLNESS

Alteration in serum thyroid hormones occurs in wide variety of illness which predominantly affects the T3 level and no intrinsic disease of thyroid gland is detected. It is variously termed as Low T3 syndrome, Sick euthryoid syndrome, Non thyroidal illness syndrome and Thyroid hormone adaptation syndrome.

This syndrome occurs in wide variety of illness as follows:

- Acute critical illness and febrile illness such as infections, myocardial infarction etc.
- Injuries such as burns, trauma, etc.
- Surgery
- Fasting
- Diabetes mellitus
- Liver disease
- Renal disease
- Ketogenic diet
- Drugs such as glucocorticoids, dopamine, phenytoin and beta blockers
- Malignancy
- Psychiatric illness

In non thyroidal illness state, initially there is decrease in serum T3 level, both total and free T3 (FT3). This is associated with increase in reverse T3 (rT3).

As illness progresses, there is decrease in serum T4 also, a state called "Low T3, T4 syndrome". Although total T4 level decreases, the free T4 (FT4) remains normal or slightly reduced. In spite of this reduced

T3 and T4 level, serum TSH level remains normal or reduced, by which it is differentiated from primary hypothyroidism. However, many studies have showed slight elevation of TSH level in Non thyroidal illness in the absence of hypothyroidism.

THYROID FUNCTION TESTS

TSH is released from the anterior pituitary under positive regulation from TSH-releasing hormone (which is released from the hypothalamus) and negative feedback from the thyroid hormones tri-iodothyronine (T3) and thyroxine (T4). Most clinical laboratories use TSH assays that have a limit of detection of <0.02 mU/L and that, therefore,are suitable for identifying the majority of cases of both hypothyroidism and hyperthyroidism[37].

T4 is secreted from thyroid follicular cells during hydrolysis of the thyroid hormone storage glycoprotein, thyroglobulin. In serum, 99.9% of T4 is bound to thyroxine-binding globulin and other proteins, although only the free hormone is available for cell uptake and is thus biologically active. Because of the extensive protein binding, total T4 levels may correlate poorly with disease states; for example, estrogen use, pregnancy, acute hepatitis, and certain genetic abnormalities are associated with increased thyroxine-binding globulin

concentrations and may result in a T4 level that is misleadingly elevated. Conversely, in clinical situations those are associated with low thyroxine-binding globulin concentrations. Current guidelines recommend measuring the T4 level only after the TSH level is found to be abnormal or if central hypothyroidism or thyroid hormone resistance is suspected [38].

Most T3 is produced by systemic 5_-deiodination of T4;only 20% of T3 is released from the thyroid . A second T4 deiodination pathway leads to the production of an inactive hormone, 3,3_,5_-triiodothyronine or reverse T3. Although T3 is the most active form of thyroid hormone, the clinical utility of measuring T3 is limited to a few situations. In patients with a low TSH level, T3 should be measured

(1) to evaluate for isolated elevation of the T3 level (i.e., T3 toxicosis),

(2) to determine the severity of thyroid disease, or

(3) to monitor response to antithyroid therapy. However in patients with an elevated TSH level, T3 concentrations are initially maintained in the normal range by increased peripheral conversion of T4 to T3; therefore, this measurement has reduced sensitivity for the diagnosis of hypothyroidism[39].

HIV AND THYROID

While baseline thyroid profiles in HIV infection may remain normal, it becomes abnormal during the course of disease. Among individuals infected with HIV, 1%–2% experience overt thyroid disease, and 35% may have subtle abnormalities in thyroid function test findings.[36]

In patients with advanced HIV disease, a variety of systemic opportunistic conditions that infect or infiltrate the thyroid can decrease or increase T4 secretion[40] Cases of thyroiditis have been reported in association with Pneumocystis jiroveci infection, Cryptococcus neoformans infection, visceral leishmaniasis, CMV infection and suppurative bacterial infection of the thyroid[41,42,43&44]. These infiltrating conditions lead to destructive thyroiditis, which is usually accompanied by neck pain, thyroid enlargement, and increased thyroxine release. After treatment of the infection, thyroid function can return to normal, but it should be closely monitored until it does so. In addition, both lymphoma and Kaposi sarcoma can infiltrate the thyroid and impair function. Less requently, hypothalamic – pituitary failure due to central nervous system infections is involved. Symptomatic thyroid infection or infiltration has always been uncommon, and in countries where HAART is available, it has become extremely rare.

A retrospective and prospective study, from India, of thyroids obtained at autopsy found high incidence (35%) of abnormal thyroids and tuberculosis was the predominant finding in these specimens. [45]

Overt hypothyroidism is common both among the general population, in which 0.3%[46]of persons are affected, and among HIV-infected individuals, among whom small studies have reported a prevalence of 0%–2.6%.[47&48]

Low FT4 levels with concurrent normal TSH levels are found frequently among HIV-infected individuals, with a reported prevalence of 1.3%–6.8%[36,47&49] An even higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality[50].

Among patients with HIV infection and subclincal hypothyroidism, anti-thyroid peroxidase antibodies are rarely identified, suggesting that the etiology may not be autoimmune [51].

Among HIV-infected populations, the highest frequency of nonthyroidal illness was reported among patients with terminal AIDS before the HAART era, with as many as 16% of patients affected. During severe illness, including advanced AIDS, 5_-deiodination of

T4 declines, leading to decreased T3 production and reverse T3 metabolism, and 5-deiodination of T4 to inactive reverse T3 is increased, creating a pattern of thyroid testing that suggests thyroid dysfunction. This pattern, however, is a result of the physiological response to illness and not a result of abnormal thyroid function.

The most common thyroid function pattern during non thyroidal illness is reduced T3 level, elevated reverse T3 level, variable FT4 level, and relatively normal or decreased TSH level, depending on the severity of illness, although a smaller increase in the reverse T3 level has been observed among patients with advanced AIDS[52] Because chronic HIV infection itself can lead to nonthyroidal illness, this diagnosis should always be considered for patients with uncontrolled HIV infection and abnormal thyroid function test results.

Decreased CD4 cell count has been observed in patients who had low FT3 levels but who also exhibited weight loss, which points to NTI[53] Collazos et al. found a correlation between FT4 levels and CD4 cell counts in patients treated with HAART. They hypothesized that the correlation might be mediated by cytokines, especially IL-2. The infusion of IL-2 in asymptomatic HIV-infected patients resulted in transient increases in TSH, free thyroxine and CD4 cell counts [54]

Experimental studies on the influence of thyroid hormones on the course of an alloimmune response revealed Murine T_3 and T_4 levels were increased a few days after the immunization of mice with allogeneic lymphoid cells. Besides in vivo treatment with T_4 was shown to increase alloantibody titers during the early stages of alloimmunization and to enforce lymphoid proliferation in vitro in a mixed lymphocyte reaction. Conversely, lowering thyroid hormone serum levels by propylthiouracil treatment negatively modulates the humoral and cellular alloimmune responses. The evidence here points to the existence of a bidirectional communication between both systems [55]

Mean 24-hour TSH levels were increased in HIV patients, associated with increased mean TSH pulse amplitude and TSH responsiveness to TRH. No differences were observed between asymptomatic HIV-seropositive and AIDS patients. In conclusion, there is a hypothyroid-like regulation of the pituitary-thyroid axis in stable HIV infection, which differs distinctly from the euthyroid sick syndrome in non-HIV-nonthyroidal illnesses. These changes in thyroid hormones might be caused directly, as an HIV-associated impairment in thyroid function, or indirectly, as an adaptation to counteract hypermetabolism in HIV infection[56]

HAART AND THYROID

Several complications related to HAART have been described, including thyroid dysfunction, but the mechanism by which HAART causes these alterations remains unknown, even if is probably multifactorial with the HIV infection also being involved. Regarding thyroid function during HAART, an increased prevalence of thyroid function parameter abnormalities have been reported by authors and these refer in most cases to asymptomatic patients, in particular

those with subclinical hypothyroidism, although groups of patients with clinically evident hyperthyroidism, in particular Grave's disease, have also been observed. In some cases hyperthyroidism has been considered as late manifestation of immune reconstitution caused by HAART. Autoimmune thyroiditis has also been implicated in the development of subclinical hypothyroidism caused by long term HAART.

Despite the autoimmune etiology of most cases of hypothyroidism, onset of Hashimoto thyroiditis does not appear to be common during HAART-associated immune reconstitution. Stavudine use, however, has been associated with subclincal hypothyroidism in some, but not all, studies. The mechanisms underlying this association are unclear and deserve further investigation.

One postulated hypothesis is that the retinoid X receptor-selective ligand suppresses thyrotropin secretion; this higher prevalence could be related to the retinoid like effects of PIs. Another hypothesis could be related to the lipodystrophy present in most of these patients. Lipodystrophy could simulate a fasting situation leading to a fall in the leptin level responsible for the suppression of the thyroid axis[57]

In adults, isolated low FT4 levels have been associated with receipt of didanosine, stavudine, and ritonavir. Higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality. Graves' disease, an autoimmune disease that leads to the production of anti-TSH receptor antibodies, is the leading cause of hyperthyroidism both in the general population and in HIV infected individuals.[58] In persons with HIV infection, Graves' disease may occur after immune reconstitution from HAART. Graves' disease is most commonly diagnosed 12–36 months after HAART initiation.

The conclusions from Iranian study was different from others which stated that age, sex, HAART, mean CD4- cell count, duration of HIV infection, HCV co-infection, and opportunistic infections were not significant risk factors of hypothyroidism in HIV-infected

patients. The occurrence of hypothyroidism may be related to other factors or HIV infection itself. Therefore, hypothyroidism should be considered in all HIV-infected patients[59].

Beltran et al proved that none of the investigated mechanisms is able to explain the occurrence of hypothyroidism in HIV patients receiving highly active anti-retroviral therapy except the anti-retroviral treatment. In light of the absence of autoimmunity, the normal adenohypophysis and thyroid responses to thyrotropin-releasing hormone, central hypothyroidism is suspected and could explain Low T4 and high TSH levels. Underlying mechanisms need further exploration.

Clinical syndromes involving decreased thyroid hormone levels

Condition	TSH	FT4	FT3	COMMENTS
Overt hypothyroidism	↑↑	↓	↓	May be associated with anti TPO
Subclinical hypothyrodism	↑	N	N	More common during HAART; usually asymptomatic; rarely associated with anti-TPO in HIV- infected patients; health care providers should also consider recovery from nonthyroidal illness
Isolated low FT4	N	↓	N	More common during HAART; Usually asymptomatic and of unclear significance; health care providers should alsoconsider nonthyroidal illness
Central hypothyrodism	↓	↓	↓	Very rare; when symptoms of dysfunction in other endocrine systems are usually present (pan-hypopituitarism or hypothylamic dysfunction)
Nonthyroidal illness	N/↓	N/ ↓	↓	Occurs during severe acute illnes or cachexia as a result of down-regulation of conversion of T4 to T3

MATERIALS AND METHODS

MATERIALS AND METHODS

Place of study : Department of Medicine,
Kilpauk Medical College and Hospital, Chennai

Collaborating department : ART centre and Department of Biochemistry, Kilpauk Medical College

Duration of the study : November 2009 - October 2010

Type of study : Cross sectional study

Conflict of Interest : None

Ethical Committee Approval : Obtained

Study population :

In the above mentioned study period, 110 patients were chosen randomly who were either Pre ART HIV positive individuals (n=49) or HIV patients on HAART (n=61) by strictly adhering to inclusion and exclusion criteria.

Inclusion criteria

- All HIV infected patients both Pre ART and individuals on HAART.
- Patients of more than 18 years

Exclusion criteria

- Patients less than 18 years of age
- Patients with known thyroid dysfunction
- Patients on drugs known to cause thyroid dysfunction
- Pregnancy
- Severely ill patients
- Patients with renal and hepatic dysfunction
- Pituitary and hypothalamic disorders

CONSENT

All patients gave written informed consent.

METHODOLOGY

Detailed history, symptoms and signs of thyroid dysfunction were noted. History of medication, and anthropometric measurements like height, weight, waist circumference were noted in a standard proforma. All patients were completely examined and routine urine and blood investigations were taken to rule out comorbid conditions. Patients were staged in accordance to WHO guidelines and grouped accordingly.

The following investigations were done

- Thyroid profile (Free T4, FreeT 3 and TSH)
- Renal Function Test (Sugar, Urea, Creatinine, and Electrolytes)

- ❖ Liver Function Test (S.Bilirubin, SGOT, SGPT, SAP, Total Protein and Albumin)
- ❖ Complete Blood Count (Total Count, Differential Count, ESR,
- ❖ Hemoglobin, PCV and Platelets)
- ❖ Electrocardiogram and Chest X-Ray – PA view
- ❖ CD4 Count

Detection of HIV infection

The detection of HIV infection was done by ELISA (Enzyme Linked Immuno Sorbent Assay). The kit contains antigens for both HIV-1 and HIV-2. These kits use both natural and recombinant antigens.

CD4 cell count

CD4 cell count was done by flow cytometry. The FACS count method was used and laser principle technique was applied in it.

Thyroid Hormone Assay

The thyroid hormone assay (TSH and FT4) were done by Chemiluminescence Immuno Assay (CLIA) using ADVIA Centaur-equipment.

DEFINITIONS- as per recommendations of consensus statement by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. (15)

Euthyroidism

TSH : 0.34 - 4.25mU/L

FT 3 : 2.4 - 4.2 pg/ml

FT4 : 0.8 - 1.70 ng/dl

Sub clinical hypothyroidism

TSH : 4.25 - 10.0 mU/L

FT 3 : 2.4 - 4.2 pg/ml

FT4 : 0.8 - 1.70 ng/dl

Hypothyroidism

TSH : > 10.0 mU/L

FT 3 : < 2.4 pg/ml

FT4 : < 0.80 ng/dl

Hyperthyroidism

TSH : < 0.1 mU/L

FT 3 : > 4.2 pg/ml

FT4 : > 1.70 ng/dl

Isolated low FT4

TSH : 0.34mU/L - 4.25mU/L

FT4 : < 0.80ng/dl

Isolated low FT 3

TSH : 0.34mU/L - 4.25mU/L

FT 3 : < 2.4 pg/ml

Statistical analysis

Statistical analysis was done by using windows SPSS software (version 11.5). Chi square test was applied for significance. “P” value less than 0.05 was considered as significant.

RESULTS AND ANALYSIS

RESULTS

A total of 110 sero positives were taken as study group which included 61 patients on HAART and 49 patients who were pre ART.

100 normal sero negative individuals with no history of thyroid dysfunction were taken as control group.

- ❖ Majority of both the study and control groups were in the age group of 25 - 36 years.
- ❖ Majority of thyroid dysfunction was also present in the same age group mentioned above. (Table.1 and 1a)

Table. 1. Age distribution

	Age distribution				**Total**
	< 25 years	**25 - 35 years**	**36-45 years**	**> 46 years**	
HIV negative individuals	**30 (30%)**	**49 (49%)**	**17 (17%)**	**4 (4%)**	**100**
HIV positive individuals	**13 (11.8%)**	**55 (50.5%)**	**35 (31.8%)**	**7 (6.4%)**	**110**
Pre ART	7 (14.3%)	28 (57.1%)	13 (26.5%)	1 (2%)	49 (44.5%)
ART	6 (9.8%)	27 (44.3%)	22 (36.1%)	6 (9.8%)	61 (55.5%)

Table.1a. Abnormal Thyroid Function Test in HIV positive individuals

	< 25 years	**25-35 years**	**36-45 years**	**> 46 years**	**Total (41)**
ART	3 (10.71%)	14 (50 %)	10 (35.4 %)	1 (3.57 %)	28
Pre ART	2 (15.38 %)	7 (53.84 %)	3 (23.07 %)	1 (7.6 %)	13

Our study group had 54.5 % of male and 45.5 % o female. The thyroid function tests were found to be abnormal in 58.54 % of males and 41.5 % of females (Table.2.).

Table.2. Gender distribution

	Sex distribution		**Total**
	Male	**Female**	
HIV negative individuals	**55 (55 %)**	**45 (45 %)**	**100**
HIV positive individuals	**60 (54.5%)**	**50 (45.5 %)**	**110**
Pre ART	24 (49 %)	25 (51 %)	49 (44.5%)
ART	36 (59 %)	25 (41%)	61 (55.5 %)

Housewives (25.45%) and unskilled labourers (57.27%) constituted the majority of the study group in both pre ART and ART categories (Table.3.).

Table.3. Occupation

S.No.	Occupation	Pre ART individuals	ART individuals	Total
1.	Unskilled labourer	30 (61.22 %)	33 (54.09%)	63
2.	Skilled labourer	4 (8.16 %)	8 (13.11%)	12
3.	Lorry driver	3 (6.12%)	2 (3.28%)	5
4.	Commercial sex worker	-	1 (1.64%)	1
5.	Office worker	-	1 (1.64%)	1
6.	House wife	12 (24.49%)	16 (26.23%)	28
7.	Businessman	-	-	-

Heterosexual route was the most common mode of transmission of HIV infection which is about 97 – 98 % (Table.4.).

Table. 4. Route of transmission

S.No.	Route of transmission	Pre ART individuals	ART individuals
1.	Heterosexual	48 (97.9%)	59 (96.7%)
2.	Homosexual	1(2.1%)	2(3.3%)

Mean duration of HIV infection was 2.3 years in study group and the mean duration of patients with thyroid abnormality in HIV positive individuals was 3.7 years.

Opportunistic infections were observed in 25 % of patients with thyroid abnormality whereas 15 % in study group.

The commonest opportunistic infection was tuberculosis followed by oral candidiasis and herpes zoster.

In study group 25 patients (22.7 %) had abnormal TSH level. Out of which, 22 patients had TSH in subclinical hypothyroid level and 3 patients had TSH in overt hypothyroid level. In sero negative group 2 persons (2 %) had abnormal TSH value in subclinical hypothyroid range.

Table.5. TSH analysis

	TSH		**Total**
	Normal	**Abnormal**	
HIV negative individuals	**98 (98 %)**	**2 (2 %)**	**100**
HIV positive individuals	**85 (77.3%)**	**25 (22.7 %)**	**110**
Pre ART	40 (81.6 %)	9 (18.4 %)	49 (44.5%)
ART	45 (73.8 %)	16 (26.2 %)	61 (55.5 %)

Table.6. FT 3 analysis

	FT 3		**Total**
	Normal	**Abnormal**	
HIV negative individuals	**99 (99 %)**	**1 (1%)**	**100**
HIV positive individuals	**98 (80.9 %)**	**12 (19.1 %)**	**110**
Pre ART	47 (95.9)	2 (4.1)	49 (44.5%)
ART	51 (83.6%)	10 (16.4 %)	61 (55.5 %)

Table.7. FT 4 analysis

	FT 4 value		**Total**
	Normal	**Abnormal**	
HIV negative individuals	**99 (99 %)**	**1 (1%)**	**100**
HIV positive individuals	**103 (93.6 %)**	**7 (6.4 %)**	**110**
Pre ART	47 (95.9)	2 (4.1)	49 (44.5%)
ART	56 (91.8 %)	5 (8.2 %)	61 (55.5 %)

The most common thyroid dysfunction observed was subclinical hypothyroidism both in ART and pre ART group with raised TSH and normal range of FT 3 and FT 4.

Subclinical hypothyroidism was observed in 22 patients among 110 study group patients (Table.8)

Among them, 13 patients were from ART group and 9 patients from Pre ART group.

Mean TSH range was higher in ART group 6.85 µIU / ml and in pre ART group was 5.4 µIU / ml which is statistically significant. Three patients in ART group were found to have overt hypothyroidism.

Three patients were having over hypothyroidism. Among them, one patient have low FT 4 along with raised TSH and other two patients had low FT 3 with raised TSH. (Table 5,8,9)

FT 3 abnormality was found in 19.1 % of study group. In pre ART category it was 17 % and in ART category it was 83 % .

Isolated low FT 3 was the common FT 3 abnormality observed which constituted about 92 %. One patient (8 %) had raised FT 3.

Mean FT 3 was 1.15 pg/dl in pre ART group and 1.3 pg/dl in ART group. (Table 6,8,9)

FT 4 abnormality was found in 6.4 % study populations. Among them, 71.43 % were in ART group and 28.57 % were in pre ART group.

Isolated low FT 4 was found in 85.7 % patients. One patient (14.3 %) had raised FT 4.

Mean FT 4 value was 0.42 ng/dl in ART group and 0.75 ng/ dl in pre ART group. This was found to be statistically significant. (Table 7,8,9)

Table.8. Types of thyroid dysfunction in HIV positive individuals

Types of abnormality	Total cases	Pre ART	ART
Subclinical hypothyroidism	22 (53.6 %)	9 (69.2 %)	13 (46.43 %)
Overt hypothyroidism	3 (7.31 %)	-	3 (10.7 %)
Isolated low FT 3	9 (21.95 %)	2 (15.38 %)	7 (25 %)
High FT 3	1 (2.44 %)	-	1 (3.6 %)
Isolated low FT 4	5 (12.19 %)	2 (15.38 %)	3 (10.7 %)
High FT 4	1 (2.44 %)	-	1 (3.6 %)
Total	**41**	**13**	**28**

Table.9. Thyroid profile

Thyroid profile	Normal range	Pre ART	ART
		Mean value	Mean value
TSH	0.34 – 4.25	5.40	6.85
FT 3	2.4 – 4.2	1.15	1.3
FT 4	0.80 – 1.70	0.75	0.42

Majority of FT 3, FT 4 and TSH abnormality was found in WHO stage 3 and 4 in patients in ART group and in stage 2 and 3 in pre ART group which was found statistically significant.

Table.10. WHO staging of HIV individuals on ART with Thyroid Dysfunction

WHO stage	**TSH**		**FT 3**		FT 4		**Total**
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	
I	9 20%	2 12.5%	11 21.6%	-	11 19.6%	-	11
II	12 26.7%	4 25%	14 27.5%	2 20 %	16 28.57%	-	16
III	20 44.4%	6 37.5%	21 41.2%	5 50%	23 41.0%	3 60 %	26
IV	4 8.9%	4 25 %	5 9.8%	3 33 .3%	6 10.7 %	2 40%	8
Total	45 73.8%	16 26.2%	51 83.6%	10 16.4%	56 91.8	5 8.2%	61

Table.11. HIV individuals not on ART

WHO stage	TSH		FT 3		FT 4		Total
	Normal	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	
I	17 42.5%	1 11.1%	18 38.3%	-	18 38.3%	-	18
II	20 50 %	6 66.6 %	26 55.3%	-	25 53.2%	1 50 %	26
III	3 7.5%	2 22.2%	3 6.4%	2 100%	4 8.5%	1 50 %	5
IV	-	-	-	-	-	-	-
Total	40 81.6%	9 18.4%	47 95.9%	2 4.1%	47 95.9	2 4.1%	49

Thyroid function abnormality was found commonly in patients who were on the regimen AZT + 3 TC + NVP and raised FT 3 level was found in patients who was on regimen AZT + 3 TC + EFV.

Table. 12. Thyroid function test in individuals on HAART

ART	Abnormal			Normal
	TSH	FT 3	FT 4	
AZT + 3 TC + NVP	12 (31.52%)	7 (18.42%)	4 (10.52%)	16 (42.11%)
d4T + 3 TC + NVP	3 (23.08%)	1 (7.69%)	0(0)	8 (61.54%)
AZT + 3 TC + EFV	1 (10%)	2 (20%)	1 (10%)	6 (60%)

CD 4 count was < 200 in 36.1 %, 200-350 in 54.1 % under ART group where as in pre ART group 32.65 % had CD 4 count 200- 350 and 67.35 % had CD 4 count > 350.

Overt hypothyroidism was found mostly in patients with CD 4 count < 200 and subclinical hypothyroidism patients had CD 4 count between 200 - 350.

Table. 13. CD 4 count in HIV positive individuals

CD count	Pre ART	ART
< 200	Nil	22 (36.1 %)
200 - 350	16 (32.65 %)	33 (54.1 %)
> 350	33 (67.35 %)	6 9.8 %)
Total	**49**	**61**

Table. 14. Co-relation of CD 4 count with thyroid dysfunction

CD 4 count	Subclinical hypothyroidism	Overt hypothyroidism	↓ FT3	↓ FT4	↑ FT 3	↑ FT 4
< 200	8 36.4 %	2 66.6%	5 55.5 %	2 40.0 %	1 100%	1 100 %
200 - 350	12 54.5 %	1 33.3 %	3 33.3 %	3 60.0%	-	-
> 350	2 0.9 %	-	1 11.1%	-	-	-

DISCUSSION

DISCUSSION

People with HIV appear to have greater likelihood of disorders of thyroid. During HIV infections overt clinical manifestations are less common whereas subtle changes in thyroid function are found more commonly in several studies.

Grappin et al showed daily dose of both stavudine and lamuvidine were related with presence of hypothyroidism.

Beltran et al found that use of stavudine and lower CD4 count were associated with subclinical hypothyroidism.

Another study of Beltran et al showed lower levels of FT 3 with stavudine.

Use of NNRTI especially efavirenz was showed to be a significant predictor of hypothyroidism.

In JAPI 2009, an article by Gagan Jain showed significant thyroid dysfunction in HIV individuals, where in 18 % and 20 % of the study population showed ↓ FT 3 and ↓ FT 4 respectively and 24% showed ↑ TSH with significant P value < 0.05 and it had a direct co-relation with low CD4 count.

Present study was undertaken based on the above observation, in our hospital, Kilpauk Medical College Hospital, Chennai.

Age Distribution

Our study population consisted of 110 patients, chosen randomly attending the ART center adhering to inclusion and exclusion criteria (both pre ART = 49 and patients on ART=61)

The patients were divided into 4 groups as shown in Fig. 1.

The mean age group was between 25 – 35 years which constitutes about 44.3 % patients on HAART and 57.1 % of patients not on ART.

The study group was compared with 100 normal patients selected randomly with no previous thyroid dysfunction.

The comparison between these two groups the HIV positive individuals and HIV negative individuals was statistically significant with p value < 0.05 and chi square13.67.

Majority of abnormal thyroid function test was found in age group between 25- 35 years which constitutes 50 % of patients on HAART and 53.84 % of patients not on ART.

Gender Distribution

In our study the overall male population was more than

their female counterpart, with a sex ratio of 1.2 in favour of males. The prevalence of thyroid dysfunction was found to be more in male than female. There was no statistical correlation between gender and thyroid dysfunction. There are no studies available that has data available on thyroid dysfunction and gender influence in HIV patients on HAART.

The gender distribution demonstrated 60 (54.4%) and 50 females (45.5%) in our study population and thyroid abnormalities was found in 43. 3 % HIV +ve in males and 22 % HIV +ve females individuals. This was compared with normal population and was found to be statistically insignificant with p value 0.29

Occupation

In our study group unskilled labours and housewives constituted majority of the population 57.27% and 25.45% respectively,10.91 were skilled ,CSW -0.9 lorry drivers - 4.5% office workers 0.9% statistically the nature of work was not related significantly thyroid dysfunction.

Route of transmission

Most of the study population and heterosexual behaviour in our study group 97.27%.

Duration of Infection

Mean duration of HIV infection was 2.3 years in study group and the mean duration of patients with thyroid abnormality in HIV positive individuals was 3.7 years.

Opportunistic infection

Opportunistic infections were observed in 25 % of patients with thyroid abnormality whereas 15 % in study group. The commonest opportunistic infection was tuberculosis followed by oral candidiasis and herpes zoster.

Symptoms and signs

One 40 years old female patient on ART had thyroid enlargement.

Thyroid dysfunction

TSH was found to be abnormal in 25 patients among 110 study group population which constitute about 22.7%.Among 25 patients 16 were patients on HAART and 9 were pre ART individuals which was about 26.2% and 18.4% respectively. All the 25 patients had elevated TSH values.

In the normal population 2% had elevated TSH value.

Range of TSH

In ART - 4.464 – 11.371 with mean of 6.850

In pre ART - 4.977 – 6.423 with mean value of 5..4

The TSH abnormality was found to be stsistically significant with p value < 0.05.

FT 3 analysis

FT3 value was found to be abnormal in 12 patients among 110 patients which constitutes 10.9% .Among 12 patients 10 were on HAART and 2 were pre ART with constitutes 16.4% and 4.1% respectively.

FT3 was elevated in 1 patient who was on HAART and none in pre ART.

Isolated ↓FT3 was found in 7 patients on HAART and 2 patients in pre ART.2 paints on HAART with ↓ FT3 was associated with elevated TSH. This was found to be statistically significant with p vaiue < 0.05.

FT4 analysis

FT4 value was found to be abnormal in 7 HIV positive individuals among 110 patients who constitute 6.4%.5 out of the 7 patients were on HAART and 2 were in pre ART group which constitutes 8.2% and 4.1% respectively.

Isolated FT4was elevated in 1 patient on HAART

Isolated ↓FT4 was found in 3 individuals on HAART and 2 patients in pre ART group.1 patient with ↓FT4 was associated with elevated TSH.

WHO staging

Of the 110 study population 61 patients were on HAART and 49 patients were in the pre ART group.

Of the 61 patients in the HAART group

- 11 patients (18.03%) belong to WHO stage I
- 16 patients 26.23% belong to WHO stage II
- 26 patients 42.62% belong to WHO stage III
- 8 patients 13.11% belong to WHO stage IV

Majority of the FT3, FT4 and TSH abnormality was found to be in WHO stage III and IV that is TSH abnormality was found in 37.5% in stage III and 25%in stage IV.

FT3 ABNORMALITTY

- 50% in stage III
- 33% in stage IV

FT4 ABNORMALITY

- 60% -stage III

- 40%-stage IV

Of the 49 pre ART individuals

- 18 patients (36.73%) were in WHO stage I
- 26 patients (53.06%) were in WHO stage II
- 5 patients (10.2%) were in WHO stage III
- None in stage IV

Majority of FT 3, FT4 and TSH abnormality was found in stage II and III

TSH abnormality - 55.5 % stage II

FT 3 abnormality – 100 % stage III

FT 4 abnormality – 50 % ach in stage II & III

CD 4 count

CD 4 count was < 200 in 36.1 %, 200-350 in 54.1 % under ART group where as in pre ART group 32.65 % had CD 4 count 200- 350 and 67.35 % had CD 4 count > 350.

Overt hypothyroidism was found mostly in patients with CD 4 count < 200 and subclinical hypothyroidism patients had CD 4 count between 200 - 350.

Drugs and thyroid function test

Of the 61 patients who were on HAART. 39 patients (64 %) were in the (a) Zidovidine + Stavudine + Nivarapin group.

Out of this 39 patients (64 %), 12 patients (31.52%) had SH abnormality. 7 patients (18.42%) had FT 3 abnormality, 4 patients (10.52%) had FT 4 abnormality.

16 patients (42.11 %) had normal TFT

12 patients (19.67 %) were under (b) stavudine + lamivudine + Nivarapine

Of these 12 patients, 3 patients (23.08 %) had TSH abnormality

1 patient (7.67%) had FT 3 abnormality

No FT 4 abnormality was detected.

8 patients (61.54 %) had normal TFT

(C) 10 patients (16.39 %) were in the zidovidine + stamivudine + efavirenz therapy

1 patients (10 %) had TSH abnormality

2 patients (20 %) had FT 3 abnormality

1 patients (10 %) had FT 4 abnormality

6 patients (60%) had normal TFT

CONCLUSION

CONCLUSION

- Thyroid abnormality especially subclinical hypothyroidism is more prevalent in HIV positive individuals compared to normal sero negative individuals.

- All forms of thyroid dysfunction were observed more in patients on HAART than in pre ART individuals.

- Thyroid abnormality was found more in males in our study group.

- Majority of thyroid abnormality was found in the age group of 25 – 35 years.

- There was significant inverse correlation between CD 4 count and thyroid abnormalities. Decline in CD 4 count was associated with increased incidence of thyroid abnormalities.

- There was significant correlation between duration of HIV infection and prevalence of thyroid dysfunction which was found more in patients with longer duration of HIV infections.

- Thyroid abnormality was found more in advanced stage of disease

who were in WHO stage III and IV.

- Heterosexual route was the common route of transmission.

- Tuberculosis was the most common opportunistic infection.

- Thyroid abnormality especially subclinical hypothyroidism was common in the HAART group under the Ziduvidine + stamivudine + nevarapine regimen.

- Screening of thyroid parameters is warranted in this population in view of increasing prevalence in the study population.

LIMITATIONS

- The sample size was small
- Thyroid antibodies were not measured
- Follow up study was not done. So incidence of thyroid abnormalities with previous normal function could not be studied.

ANNEXURES

PROFORMA

NAME		HOSTITAL No:	SERIAL NO
AGE		HEIGHT	WHO
SEX		WEIGHT	EDUCATION
OCCUPATION		BMI	ADDRESS
MARITAL STATUS	:		
SEXUAL EXPOSURE	:		
OTHER RISK FACTORS	:		
PARTNER'S HIV STATUS	:		
DURATION OF HIV INFECTION	:		
AGE AT FIRST SEXUAL EXPOSURE	:		
RECENT EXTRA MARITAL EXPOSURE	:		
PREVIOUS STD'S	:		
PRESENT STD'S	:		
SMOKING	:		
ALCOHOL	:		
DM	:		
HT	:		
PREVIOUS THYROID DYSFUNCTION	:		
H/O ATT	:		
PRESENTING COMPLAINTS			
TIREDNESS / WEAKNESS/ HYPERACTIVITY	:		DRY SKIN:
COLD / HEAT INTOLERANCE			HAIR LOSS:

DIFFICULTY IN CONCENTRATION/POOR MEMORY	:	BOWEL DISTURBANCES:
WEIGHT GAIN / LOSS APPETITE	:	DYSPNOEA:
HOARSENESS OF VOICE	:	MENSTRUAL PROBLEM:
PARESTHESIA	:	
EXAMINATION	:	
PALLOR	:	
JAUNDICE	:	
CYANOSIS	:	
THYROID SWELLING	:	
CLUBBING	:	
PEDAL EDEMA	:	
LYMPHADNOPAHY	:	
BP	:	
PR	:	
RR	:	
TEMPERATURE	:	
JVP	:	
OPPORTUNISTIC INFECTIONS	:	
CVS	:	
RS	:	
ABDOMEN	:	
CNS	:	

INVESIGATION

HEMOGRAM	**:**	**CD 4 COUNT**
HB %	**:**	
TOTAL COUNT	**:**	
DIFFERENTIAL COUNT	**:**	
ESR	**:**	
PCV	**:**	
PLATELET COUNT	**:**	
ECG	**:**	
CHEST X RAY	**:**	
<u>THYROID FUNTION TEST</u>	**:**	
SERUM FREE T 3	**:**	
SERUM FREE T 4	**:**	
TSH	**:**	
<u>RENAL FUNCTION TEST</u>	**:**	
BLOOD SUGAR	**:**	
BLOOD UREA	**:**	
SERUM CREATININE	**:**	
SERUM ELECTROLYTES	**:**	
<u>LIPID PROILE</u>	**:**	
TOTAL CHOLESTROL	**:**	
TRIGLYCERIDES	**:**	
HDL	**:**	
LDL	**:**	
VLDL	**:**	

LIVER UNCTION TEST :

SERUM BILIRUBIN :

SGOT :

SGPT :

SAP :

TOTAL PROTEIN :

A/G RATIO :

ABBREVIATIONS

FT4/T4	**:**	Free Thyroxine / Thyroxine
TSH	**:**	Thyroid Stimulating Hormone
FT3/T3	**:**	Free Triodothyronine / Triodothyronine
HIV	**:**	Human Immuno deficiency Virus
AIDS	**:**	Acquired Immuno deficiency Syndrome
CD	**:**	Cluster differentiation
HAART/ART	**:**	Highly Active Anti Retroviral Therapy
PRE ART	**:**	HIV Patients not on Anti Retroviral Therapy
NTI	**:**	Non Thyroidal Illness
TO	**:**	Thyroid peroxidase
NRTI	**:**	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	**:**	NonNucleoside Reverse Transcriptase Inhibitors
PI	**:**	Protease Inhibitor

S.No	Hospital No.	Age	Age Group	sex	occupation	WHO	route of transmission	CD4 count	Duration of illness	BMI	Opp.iinf	ART	Throid dusfunction symptoms	Thyroid enlargement	TSH	Ft3	Ft4	Lipid profile	RFT	LFT	TSH - AB/N	FT3 AB/N	FT4AB/N
1	953	57	4	M	1	III	1	259	2	19	5	3	1	N	0.814	3.21	1.322	1	N	N	0	0	0
2	2769	39	3	F	6	II	1	315	3	21	5	0	1	N	5.408	3.832	1.53	1	N	N	1	0	0
3	773	26	2	M	1	II	1	324	2	21	1	1	1	N	1.895	2.621	0.86	1	N	N	0	0	0
4	688	30	2	M	1	I	1	293	3	22	1	1	1	N	1.378	1.264	0.88	1	N	N	0	1	0
5	1912	22	1	F	6	I	1	763	1	22	1	0	1	N	0.813	3.329	1.049	1	N	N	0	0	0
6	972	46	4	M	2	II	1	288	3	20	1	0	1	N	2.344	3.819	0.779	1	N	N	0	0	1
7	1594	33	2	M	1	III	1	356	1	22	5	0	1	N	5.159	3.6	1.549	1	N	N	1	0	0
8	859	50	4	F	6	III	1	198	3	23	3	1	1	Y	8.679	1.3	0.84	1	N	N	1	1	0
9	2672	45	3	F	6	III	1	483	1	23	1	0	1	N	4.032	2..927	0.956	1	N	N	0	0	0
10	793	23	1	F	6	II	1	368	33	25	1	2	1	N	3.5	2.983	0.9	1	N	N	0	0	0
11	186	35	2	F	6	II	1	458	2	19.6	1	0	1	N	2.325	3.319	1.198	1	N	N	0	0	0
12	749	36	3	M	1	II	1	216	3	23	1	1	1	N	2.86	1.547	1.02	1	N	N	0	1	0
13	756	44	3	F	6	I	1	786	3	24.2	5	0	1	N	1.41	3.9	1.297	1	N	N	0	0	0
14	505	39	3	F	1	III	1	296	3	21	1	1	1	N	4.843	3.719	0.976	1	N	N	1	0	0
15	1896	32	2	F	1	I	1	425	2	23.6	1	0	1	N	3.497	3.392	0.976	1	N	N	0	0	0
16	1218	39	3	M	1	IV	1	173	6	19	5	3	1	N	3.968	2.82	1.821	1	N	N	0	0	1
17	439	40	3	F	5	III	1	161	3	19.5	2	2	1	N	6.416	3.158	0.8	1	N	N	1	0	0
18	281	35	2	F	6	I	1	706	3	23	1	0	1	N	1.113	2.941	0.89	1	N	N	0	0	0
19	1206	32	2	M	1	II	1	182	3	21	1	1	1	N	4.421	3.162	0.894	1	N	N	1	0	0
20	1449	20	1	F	1	II	1	356	1	21.7	1	0	1	N	3.258	3.472	0.881	1	N	N	0	0	0
21	450	20	1	M	2	III	1	108	3	20	2	1	1	N	1.665	0.912	1.538	1	N	N	0	1	0
22	1438	32	2	F	1	III	1	205	3	24.1	2	2	1	N	11.371	2.63	0.676	1	N	N	1	0	1
23	1221	38	3	F	6	III	1	52	3	22	1	2	1	N	1.57	1.106	0.934	1	N	N	0	1	0
24	1673	32	2	M	1	I	1	378	1	23.5	1	0	1	N	2.296	2.994	1.17	1	N	N	0	0	0
25	740	24	1	F	6	I	1	282	2	22	1	1	1	N	0.669	3.572	1.14	1	N	N	0	0	0

27	722	33	2	M	1	III	2	334	3	21	1	3	1	N	1.893	3.495	0.98	1	N	N	0	0	0
28	2537	26	2	M	1	I	1	752	3	24.5	1	0	1	N	1.818	4.108	1.369	1	N	N	0	0	0
29	622	46	4	M	2	II	1	238	3	19.5	1	1	1	N	1.702	3.248	1.094	1	N	N	0	0	0
30	688	30	2	M	1	IV	1	39	3	19	1	1	1	N	4.436	4.198	1.236	1	N	N	1	0	0
31	190	38	3	F	6	II	1	216	3	22	1	1	1	N	0.909	2.504	1.54	1	N	N	0	0	0
32	2729	27	2	M	1	I	2	926	3	25.5	1	0	1	N	2.892	3.975	1.036	1	N	N	0	0	0
33	930	39	3	M	1	III	1	121	3	18.6	2	1	1	N	7.464	2.714	1.465	1	N	N	1	0	0
34	2553	35	2	M	1	I	1	454	2	19.7	1	0	1	N	1.884	3.344	1.15	1	N	N	0	0	0
35	987	26	2	M	1	IV	1	282	3	18.5	1	1	1	N	9.405	3.352	0.984	1	N	N	1	0	0
36	2533	26	2	M	1	I	1	254	2	20.1	1	0	1	N	3.803	3.63	1.1	1	N	N	0	0	0
37	1174	36	3	M	1	I	1	843	2	23.2	1	1	1	N	2.04	3.564	1.308	1	N	N	0	0	0
38	1218	38	3	M	1	II	1	274	1	21.2	5	0	1	N	4.977	3.64	0.965	1	N	N	1	0	0
39	1015	33	2	M	1	I	1	293	2	19.4	1	1	1	N	5.168	2.717	0.963	1	N	N	1	0	0
40	1249	29	2	M	1	II	1	322	1	23.4	1	0	1	N	5.642	2.82	0.945	1	N	N	1	0	0
41	894	28	2	M	1	II	1	166	3	23.6	1	1	1	N	4.615	3.411	0.936	1	N	N	1	0	0
42	2105	28	2	F	1	III	1	267	3	22.5	1	0	1	N	4.052	1.026	0.926	1	N	N	0	1	0
43	792	28	2	M	1	III	1	198	3	22	1	1	1	N	2.25	3.158	0.33	1	N	N	0	0	1
44	2102	24	1	M	1	III	1	215	2	22.6	1	0	1	N	2.062	1.326	1.05	1	N	N	0	1	0
45	361	24	1	F	6	III	1	308	3	19	2	3	1	N	2.076	6.05	0.913	1	N	N	0	1	0
46	1798	32	2	M	1	III	1	288	3	23.2	5	0	1	N	6.023	3.012	1.083	1	N	N	1	0	0
47	368	47	4	M	1	III	1	394	3	24.2	1	1	1	N	3.368	4.132	1.552	1	N	N	0	0	0
48	2509	29	2	F	6	II	1	386	3	24.2	1	0	1	N	3.896	3.521	1.05	1	N	N	0	0	0
49	1113	34	2	M	1	IV	1	17	1	21.3	1	1	1	N	1.467	3.094	1.476	1	N	N	0	0	0
50	1678	32	2	M	1	I	1	348	1	23.1	1	0	1	N	1.623	3.621	1.032	1	N	N	0	0	0
51	954	39	3	M	1	IV	1	259	3	21.2	1	3	1	N	1.428	3.92	1.256	1	N	N	0	0	0
52	2431	35	2	F	1	I	1	358	2	22.4	1	0	1	N	2.403	3.467	1.139	1	N	N	0	0	0

53	1708	29	2	M	1	II	1	418	1	22.1	1	0	1	N	2.594	4.01	1.092	1	N	N	0	0	0
54	754	40	3	M	1	IV	1	246	3	22	5	3	1	N	7.544	3.292	1.603	1	N	N	1	0	0
55	2025	26	2	F	1	III	1	328	3	22.2	5	0	1	N	5.823	3.123	1.204	1	N	N	1	0	0
56	345	50	4	M	1	IV	1	161	2	21.6	1	2	1	N	2.25	3.26	1.321	1	N	N	0	0	0
57	1972	32	2	F	1	III	1	425	1	23.2	1	0	1	N	1.821	3.621	1.035	1	N	N	0	0	0
58	349	42	3	M	1	IV	1	165	3	19.2	1	2	1	N	5.232	3.282	1.524	1	N	N	1	0	0
59	1982	40	3	M	1	II	1	414	1	21.4	1	0	1	N	2.32	2.421	1.021	1	N	N	0	0	0
60	1077	40	3	F	6	III	1	233	2	26.4	5	1	1	N	1.313	3.271	1.198	1	N	N	0	0	0
61	2186	34	2	M	1	II	1	312	3	22.6	2	0	1	N	6.423	2.618	1.023	1	N	N	1	0	0
62	211	39	3	M	1	II	1	789	3	24.2	1	0	1	N	2.701	3.64	1.168	1	N	N	0	0	0
63	2329	35	2	F	6	II	1	486	1	19.8	1	0	1	N	2.621	2.521	0.986	1	N	N	0	0	0
64	783	23	1	F	1	II	1	368	2	24.1	1	2	1	N	6.611	2.869	0.968	1	N	N	1	0	0
65	2512	33	2	M	1	II	1	495	1	20.1	1	0	1	N	3.21	2.631	1.232	1	N	N	0	0	0
66	255	36	3	M	1	II	1	310	1	23.2	1	0	1	N	5.811	4.091	0.968	1	N	N	1	0	0
67	789	42	3	M	1	II	1	361	3	21.2	1	0	1	N	1.428	2.51	1.321	1	N	N	0	0	0
68	247	37	3	F	6	III	1	128	3	18.6	1	2	1	N	0.908	3.36	1.42	1	N	N	0	0	0
69	1452	28	2	M	1	II	1	328	2	23.4	1	0	1	N	3.214	3.21	1.231	1	N	N	0	0	0
70	835	27	2	M	1	III	2	124	2	23.4	1	1	1	N	1.447	3.312	0.904	1	N	N	0	0	0
71	1236	29	2	F	6	II	1	416	2	22.1	1	0	1	N	3.124	3.31	1.214	1	N	N	0	0	0
72	1189	37	3	M	2	II	1	593	3	22.7	5	1	1	N	1.383	3.732	1.607	1	N	N	0	0	0
73	1521	26	2	M	1	II	1	425	2	20.9	1	0	1	N	3.961	4.012	0.965	1	N	N	0	0	0
74	1222	42	3	M	1	I	1	261	2	21	1	2	1	N	3.773	3.616	0.927	1	N	N	0	0	0
75	2361	38	3	F	1	I	1	492	2	23.2	1	0	1	N	1.238	4.142	1.303	1	N	N	0	0	0
76	2768	36	3	F	6	II	1	365	3	3.6	1	0	1	N	2.842	2.642	1.36	1	N	N	0	0	0
77	708	36	3	M	1	III	1	183	2	22	1	1	1	N	3.057	2.653	1.684	1	N	N	0	0	0
78	2142	25	1	M	1	II	1	326	2	22.4	1	0	1	N	2.682	2.682	0.928	1	N	N	0	0	0

79	2576	25	1	F	6	IV	1	503	1	22	1	0	1	N	1.888	3.59	0.856	1	N	N	0	0	0
80	2438	32	2	F	6	III	1	429	1	21.6	1	0	1	N	3.101	3.102	1.521	1	N	N	0	0	0
81	828	35	2	F	6	II	1	247	2	23	1	1	1	N	2.403	3.467	1.139	1	N	N	0	0	0
82	2416	41	3	F	6	II	1	395	2	22.2	1	0	1	N	1.428	2.51	1.321	1	N	N	0	0	0
83	2553	35	2	F	6	I	1	1440	2	24.2	1	0	1	N	0.523	3.689	1.498	1	N	N	0	0	0
84	692	30	2	M	1	III	1	284	3	22.1	1	1	1	N	3.206	3.152	1.32	1	N	N	0	0	0
85	2220	50	4	M	1	I	1	282	2	21.6	1	0	1	N	2.447	3.592	1.39	1	N	N	0	0	0
86	358	40	3	F	6	III	1	233	2	22.1	1	1	1	N	1.313	3.271	1.193	1	N	N	0	0	0
87	1994	22	1	F	6	II	1	694	3	23.2	1	0	1	N	2.427	3.922	1.652	1	N	N	0	0	0
88	2572	42	3	M	1	II	1	302	2	22.2	1	0	1	N	2.447	3.592	1.39	1	N	N	0	0	0
89	2334	24	1	F	6	I	1	893	3	24.3	1	0	1	N	1.238	4.146	1.303	1	N	N	0	0	0
90	2418	40	3	M	1	I	1	487	3	21.3	1	0	1	N	2.427	3.922	1.632	1	N	N	0	0	0
91	1154	30	2	F	6	I	1	632	3	23.5	1	0	1	N	2.24	3.494	1.241	1	N	N	0	0	0
92	68	37	3	M	1	III	1	137	3	19	5	3	1	N	4.162	1.09	1.08	1	N	N	0	1	0
93	617	30	2	M	2	I	1	247	3	21	1	1	1	N	2.762	1.29	0.395	1	N	N	0	1	1
94	1195	29	2	F	6	II	1	247	2	22.4	3	2	1	N	1.24	2.67	0.82	1	N	N	0	0	0
95	913	34	2	M	1	I	1	238	1	20.5	1	1	1	N	5.228	3.225	1.015	1	N	N	1	0	0
96	271	26	2	F	6	II	1	295	3	23.7	2	1	1	N	2.921	2.488	1.313	1	N	N	0	0	0
97	817	36	3	F	6	I	1	289	2	25.4	1	3	1	N	3.51	2.46	0.9	1	N	N	0	0	0
98	148	30	2	M	1	III	1	292	1	19.4	5	3	1	N	2.486	2.47	1.02	1	N	N	0	0	0
99	10	38	3	F	6	II	1	242	2	21.4	4	2	1	N	3.25	3.71	0.976	1	N	N	0	0	0
100	967	29	2	F	6	III	1	249	2	19.7	1	0	1	N	2.356	3.133	0.648	1	N	N	0	0	1
101	266	28	2	F	6	II	1	123	3	19.5	1	1	1	N	6.075	3.389	0.891	1	N	N	1	0	0
102	784	32	2	M	1	III	1	141	2	20.2	1	1	1	N	1.993	1.49	0.865	1	N	N	0	1	0
103	627	41	3	M	2	III	1	172	3	21.2	1	1	1	N	5.19	2.1771	0.917	1	N	N	1	1	0
104	157	32	2	F	6	III	1	337	2	22.4	5	3	1	N	1.57	3.106	0.934	1	N	N	0	0	0

105	457	38	3	M	2	III	1	291	2	22.3	5	1	1	N	0.669	3.572	1.7	1	N	N	0	0	0
106	66	30	2	F	6	I	1	674	3	19.8	1	2	1	N	1.893	3.5	0.82	1	N	N	0	0	0
107	978	24	1	F	6	I	1	309	2	19.4	1	2	1	N	1.702	3.42	1.09	1	N	N	0	0	0
108	824	30	2	F	2	I	1	294	3	21.8	1	1	1	N	0.909	2.5	1.45	1	N	N	0	0	0
109	808	28	2	F	1	II	1	229	1	18.6	1	1	1	N	2.076	2.7	1.34	1	N	N	0	0	0
110	1014	29	2	F	1	III	1	115	2	21.2	1	1	1	N	1.556	3.28	0.716	1	N	N	0	0	1
111	781	28	2	M	1	III	1	128	3	18.5	1	1	1	N	7.534	3.45	1.015	1	N	N	1	0	0

MASTER CHART ABBREVIATION

Occupation	**:**	Unskilled labourer	:	1
		Skilled labourer	:	2
		Lorry driver	:	3
		Commercial sex worker	:	4
		Office worker	:	5
		House wife	:	6
		Business man	:	7
Route of transmission	**:**	Heterosexual	:	1
		Homosexual	:	2
Opportunistic infections	**:**	Nil	:	1
		Oral candidiasis	:	2
		Candidiasis other sites	:	3
		Herpes zoster	:	4
		Tuberculosis	:	5
Duration of HIV infection	**:**	< 1 years	:	1
		1-3 years	:	2
		> 3 years	:	3
ART drugs	**:**	AZT	:	Zidovudine
		3TC	:	Lamivudine
		NVP	:	Nevirapine
		EFZ	:	Efavirenz

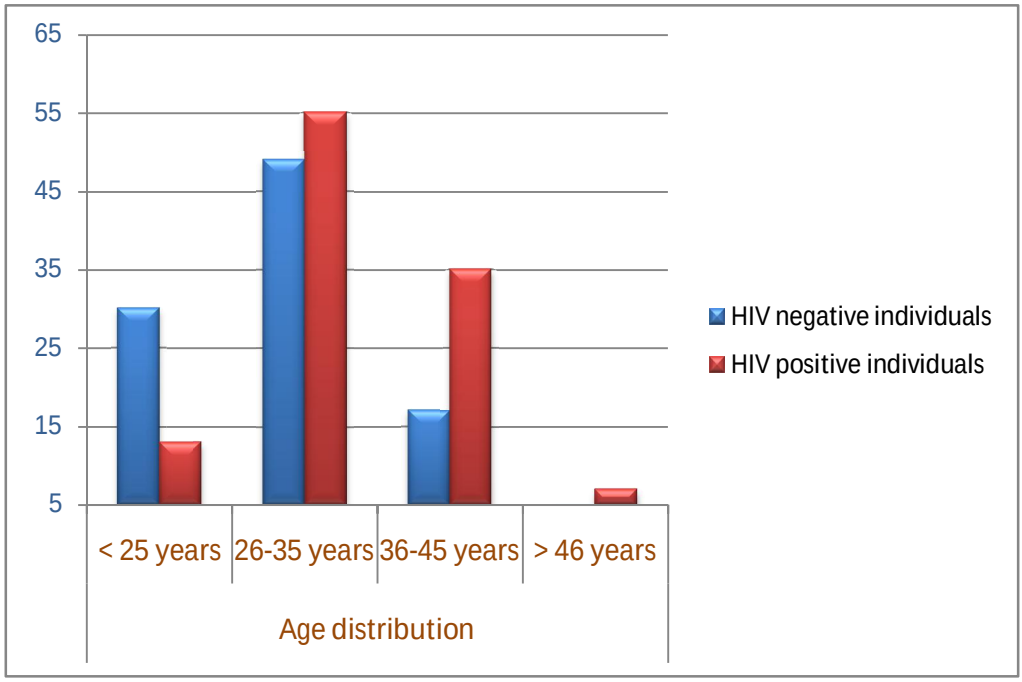

Figure.1. Age distribution

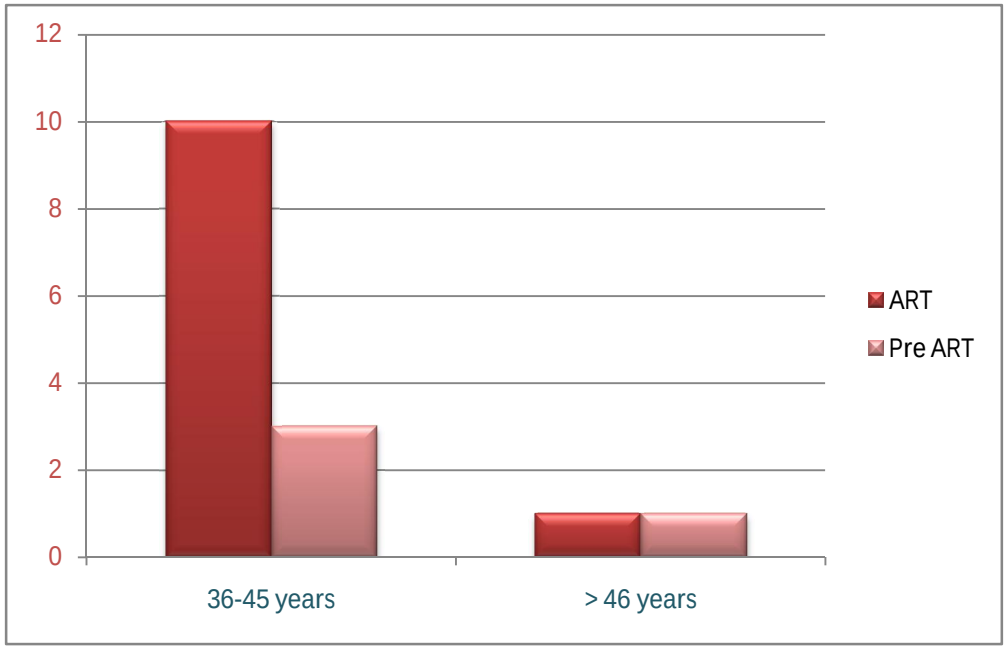

Figure. 1a. Abnormal thyroid functional test in HIV positive individuals

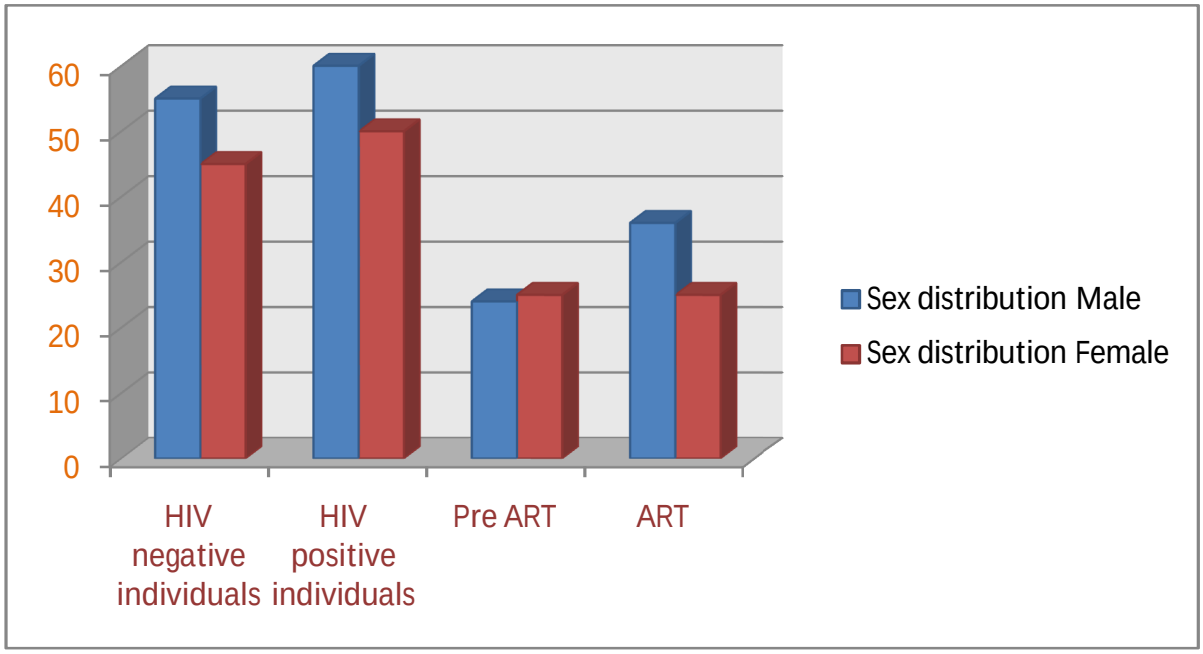

Fig.2. Sex distribution

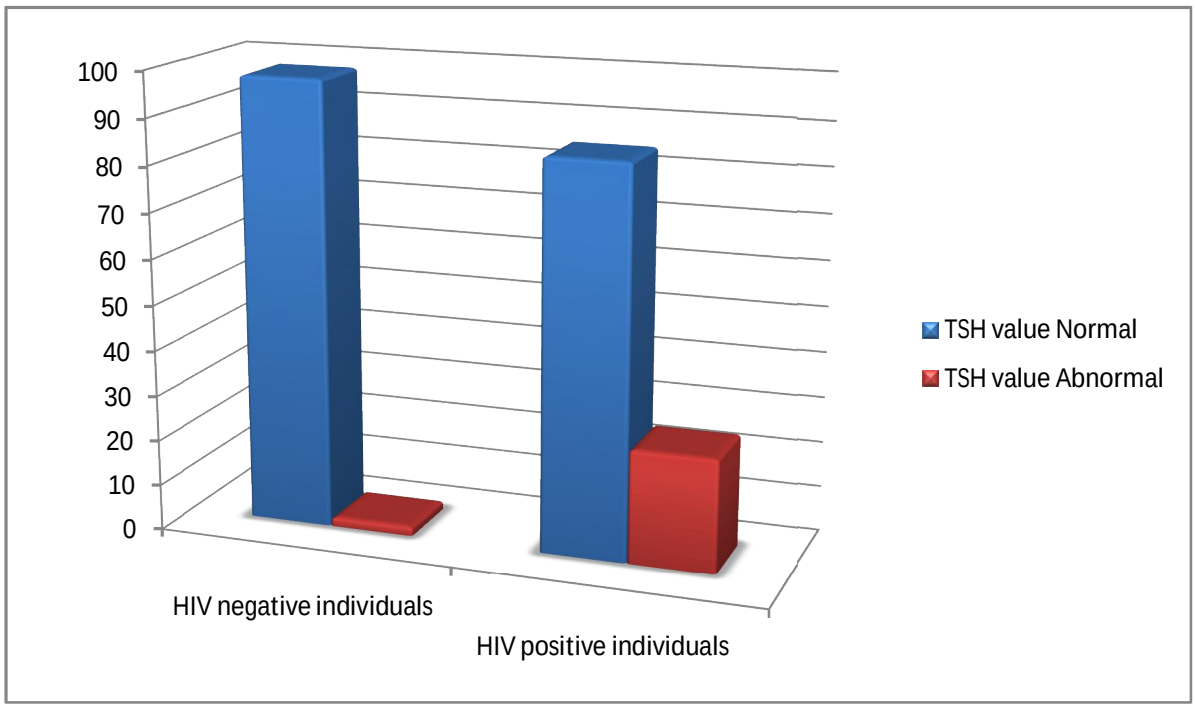

Fig.3. TSH analysis

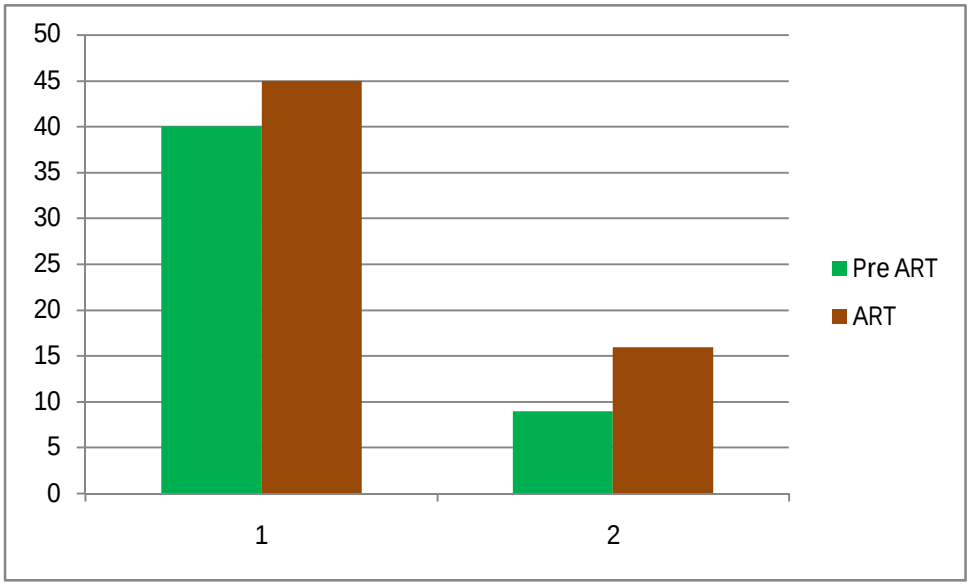

Figure. 3. TSH in pre ART and ART

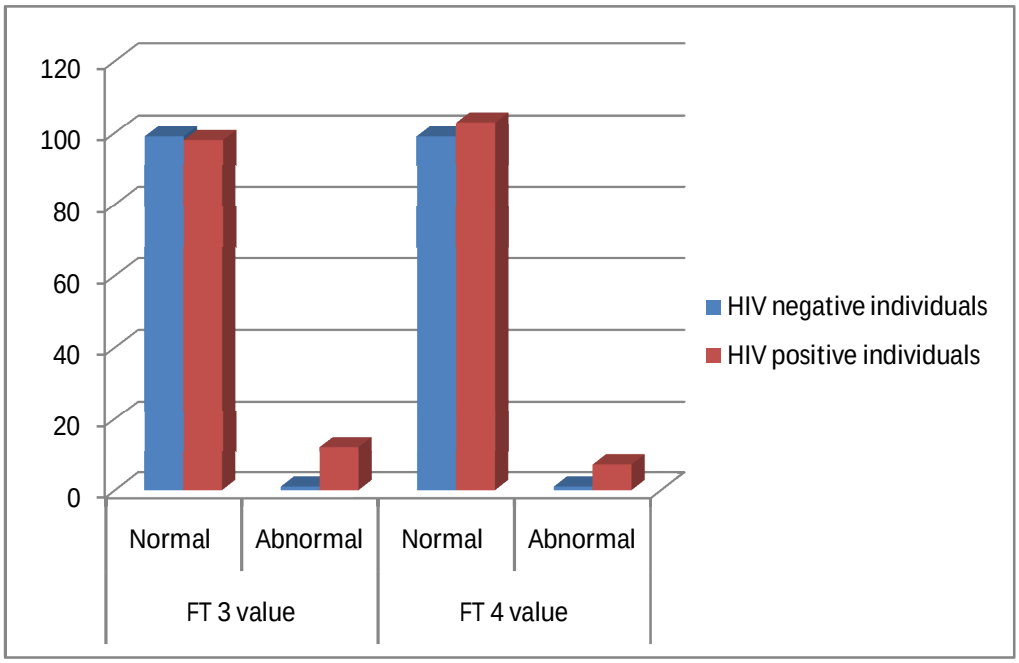

Figure.4. FT 3 and FT 4

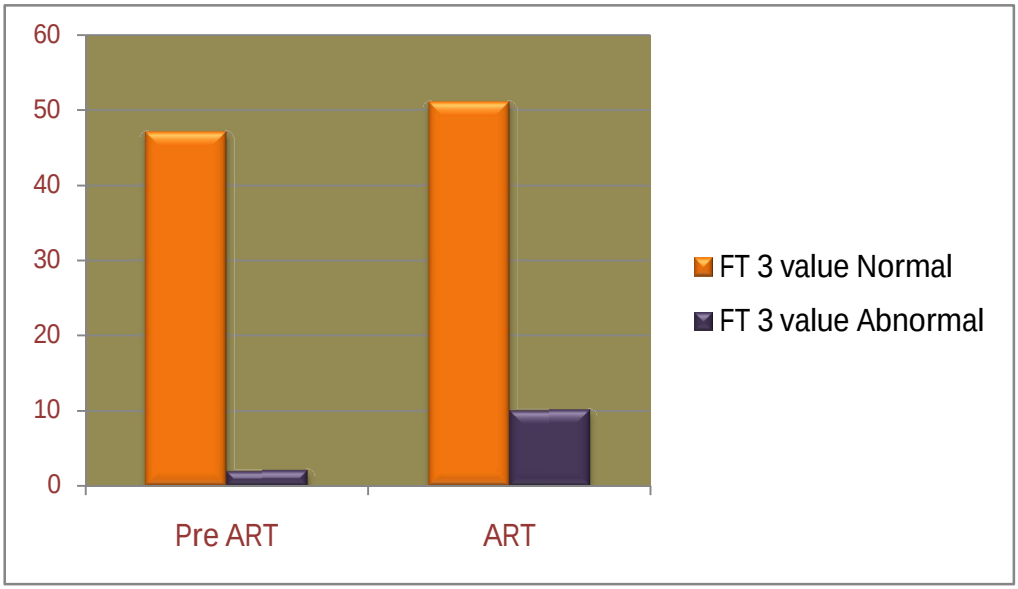

Figure.4. FT 3 and FT 4

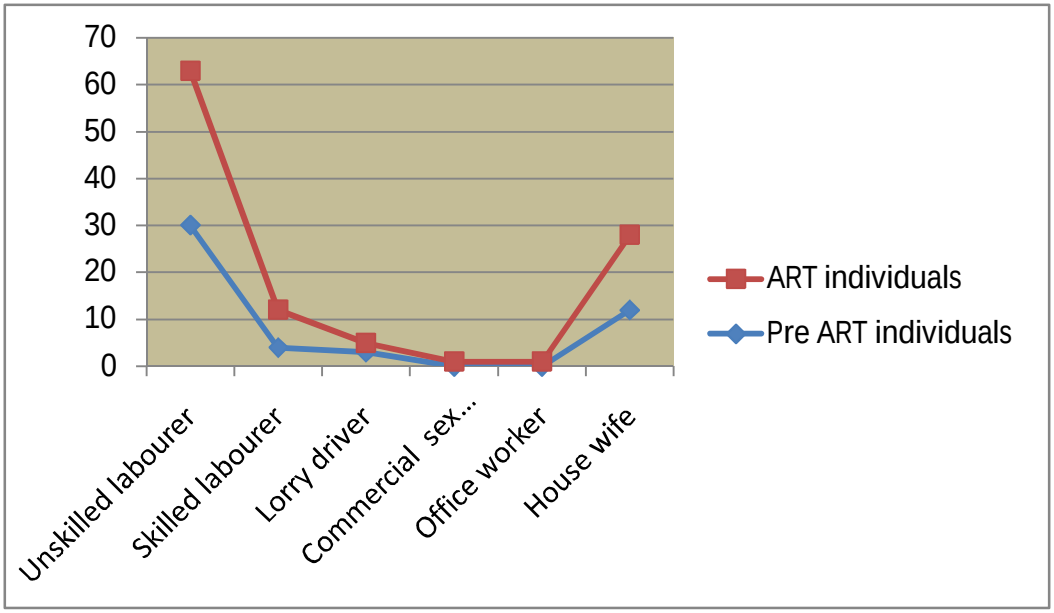

Fig. 5. Occupation

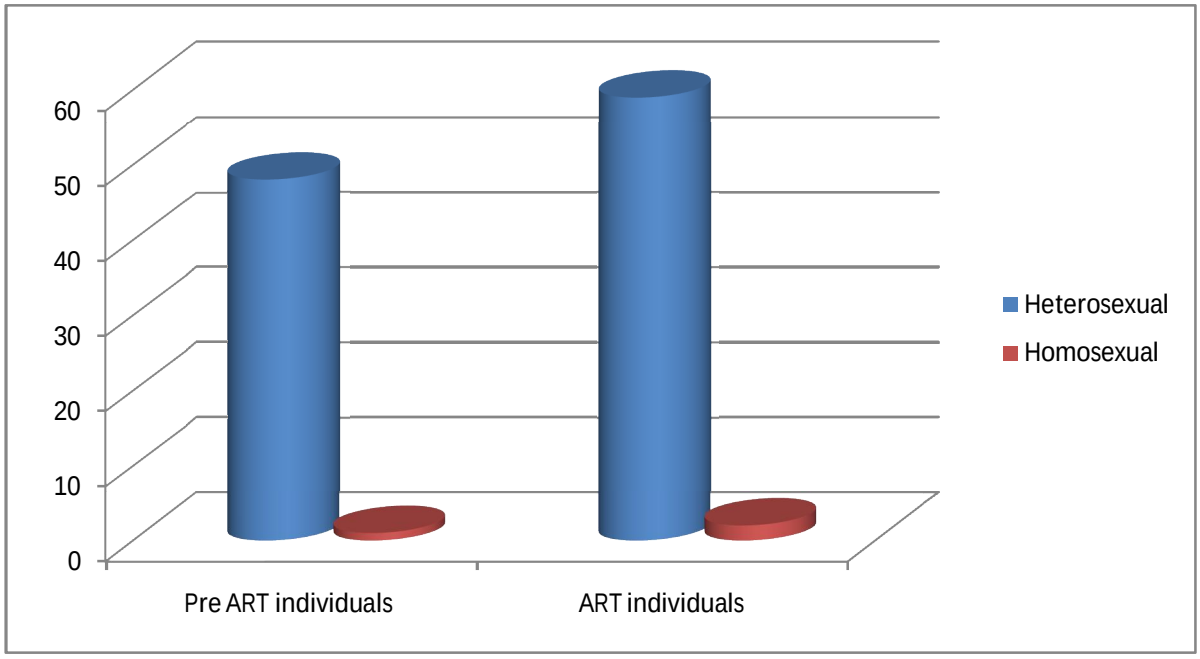

Fig. 6. Route of transmission

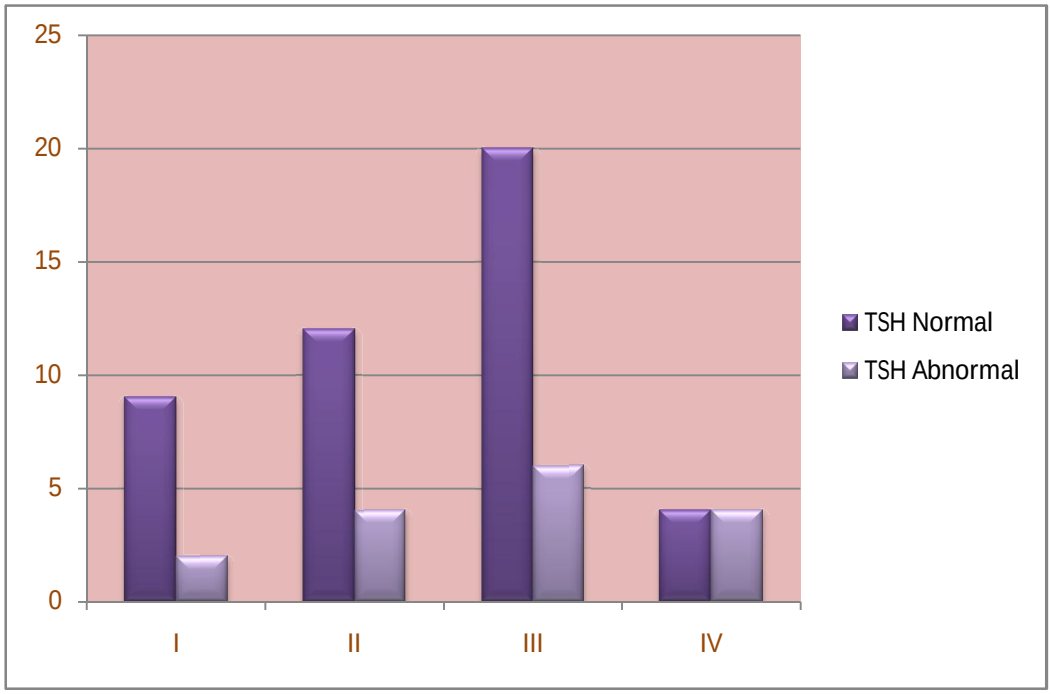

Fig.7. WHO stage and TSH abnormality on HAART

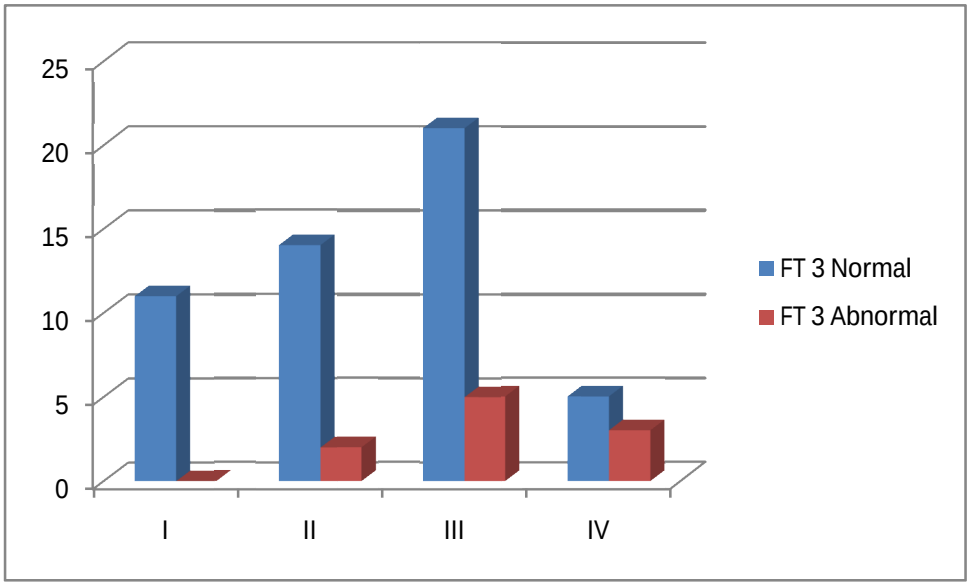

Fig.7a. WHO stage and FT 3 abnormality in patients on HAART

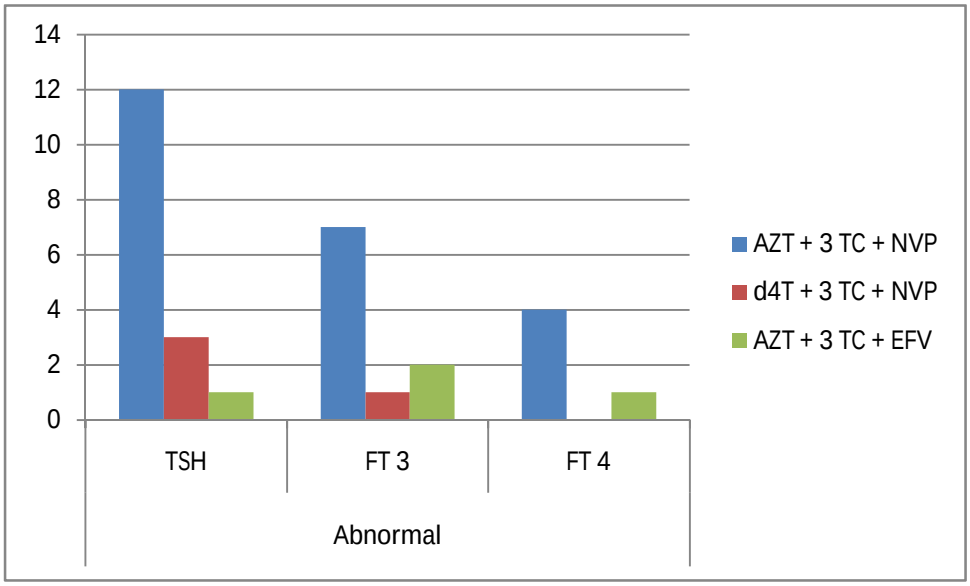

Fig. 8. Thyroid function test in patients on HAART

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BIBLIOGRAPHY

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